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A comprehensive review of bioactive glass: synthesis, ion substitution, application, challenges, and future perspectives

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ABSTRACT

Bioactive glass (BG) and glass-ceramics (GC) have been employed for bone treatment tissue engineering applications. Bioactive glasses/bioglasses can be considered promising materials for bone-regenerative scaffolds fabrication, owing to the adaptable properties that make them appropriately be designed regarding their composition. The essential properties of bioactive glasses, enabling them to be applied in the engineering of bone tissue, can be explained as their potential to augment differentiation osteoprogenitor and cells of mesenchymal stem cells, enzyme activity, osteoblast adhesion, and revascularization. Much research is conducted for the development of phosphate glasses, borate/borosilicate BGs, and silicate. Accordingly, some metal-based glasses have also been surveyed for tissue engineering uses, technologically and biomedically. Many rare elements can also be incorporated in the network of the glass to achieve promising properties, possessing a positive influence on the associated angiogenesis and/or remodeling of bone. This review motivates for providing an overview toward bioactive glasses' general requirements, composition, production, and impact of ion substitution on bioactive glass. Attention has also been given to developments of bioactive glass applications in bone grafting, bone regeneration, drug delivery, dental implant coatings, antibacterial agents, and soft tissue engineering as well as challenges and future perspectives.

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1. Introduction

Glass has been used for centuries by humans, for many applications like the natural glass in arrowheads and tools, and the early human-made drinking vessels and glass beads in Egypt and Mesopotamia. However, the recent uses of glass are expanded to telecommunicational uses as fibers, chemical reactions of glassware, and optical and architectural (e.g., window and glass facades) fields [1].

Damaged bone tissues can be reconstructed or repaired by utilizing bioactive glasses due to their osteoinductivity and osteoconductivity. Their reactive surfaces lead to biological activity induction and strong bond formation with living tissue like bone [2]. They are employed in other areas such as engineering of soft tissue [3-8], antibacterial factors [9-14], coatings of the dental implant [15-22], drug delivery [18-20, 23, 24], regeneration of bone [14, 25], and grafting of bone [6, 8, 26, 27].

A significant property of BG is its ability to the enhancement of differentiation of mesenchymal stem cells, enzyme activity, osteoblast adhesion, and revascularization to apply in bone tissue engineering. The first synthesis of BG was discovered by Larry Hench that was related to the bone that not only attaches with bone but releases dissolution ions (including calcium ions and soluble silica) also which stimulate cells of genetic level, developing bone enhancement (osteogenesis) [28, 29]. Furthermore, they can be the desired candidate for coatings/filter materials applied in polymer frameworks. However, the BG features should be assumed because of granulates of various sizes and aspects of their particles/powders of different sizes and shapes. Additionally, fabrication of bioactive composites should be evaluated in order to toxicity risk, owning lower element release rather than their biologically safe levels, render no or slight cytotoxicity. Although BG has been developed via a combination of biologically active elements like zinc (Zn), copper (Cu), magnesium (Mg), and strontium (Sr) to impart special biological applications and also to develop the therapeutic behavior [30-34]. The ion substitution turns into a novel technique in the fabrication of novel BG to affect the material and therapeutic features of BG. Du et al. reported the issues and advantages of metal compounds applied as biomedical implants and the improving approaches of using coatings of bioactive glass for biomedical functionalities [35, 36].

Additionally, various methods have been applied to the fabrication of BG materials like microwave manufacturing [37-39], flame spray [40-42], sol-gel [30, 34, 43-45], and melt quenching [45-48]. BG materials can provide suitable compatibility for structures with no disadvantageous impact on the living tissues. We can fabricate especially aimed BG via the development of primary BG composite and also altering the synthesis conditions that can be sol-gel or melt quenching [43, 49].

Furthermore, the bioactive glass nanoparticles (BGN) based on silicate fabricated by sol-gel strategies, owning various catalysts for launching the hydrolysis and condensing the precursors of silicate and also the combination of sol-gel chemistry by other methods are studied. The mechanism and condition of various fabrication techniques are prepared and explained in detail [50, 51]. The fundamental aspects of GC condition and enhancement with sinter-crystallization of powdered glasses or controlled heat treatments of monolithic pieces were reported by Montazerian et al. [52]. A number of research have been conducted on the development of phosphate glasses and silicate, borate/borosilicate BGs. A remarkable amount of metallic glasses have been evaluated for technological and biomedical fields of tissue engineering [43, 53, 54].

Hence, numerous trace elements have been combined in the glass structure to achieve desirable features, owning advantageous influence on related angiogenesis and/or remodeling of bone. Although various researchers have reported the reviews of BG, topics like ion substitution, future perspectives of BG briefly and in one paper have not been investigated yet. First, a brief overview of the BG characteristics, structure, and applications is reported. Next, the impact of ion substitution on BG is investigated. Then, advances of BG in different applications are reviewed. Finally, the future and challenges of BG are explained.

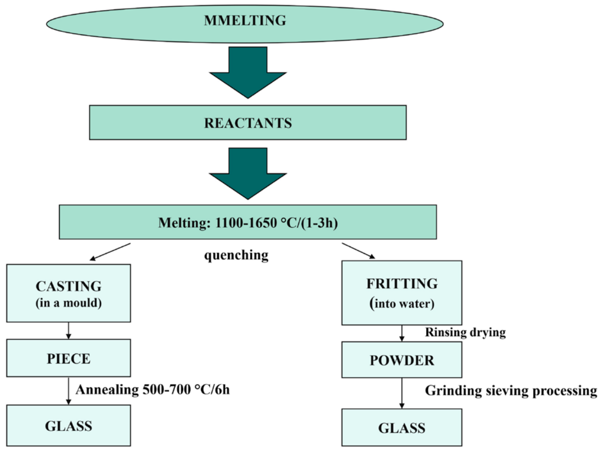

Fig. 1. The schematic of the melt-quenching process.

2. Synthesis of bioactive glass

2.1. High-temperature melting (melt quenching)

The melt-quench procedure has been used for the synthesis of glasses with desirable sizes. Nowadays, the most practical glasses (more than 99%) are fabricated by this method. The fusion of raw material crystals (carbonates, acids, or oxides) obtains a viscous liquid, then melt casting by rapid quenching. The benefits of the melt quench method in comparison to other techniques are listed: (i) synthesis glass is free from strains and fracture; (ii) the easy way to dope active ions (transition metals and rare earths); (iii) because of nonstoichiometry of batch calculation, there is flexibility to composites; (iv) achievement of large structures compared to a single crystal; (v) achievement of the highly flexible geometrical shape of glass; (vi) well-known synthesis strategies. Due to these advantages, the melt quench technique become a more popular ones that are extensively applied to oxide/oxyhalide glasse synthesis [55]. The conventional melting technique has mostly been used for BG synthesis and applied as the cost-effective procedure for mass production [56]. Glass is achieved via fusing the raw material combination and further solidification using quenching into glass frits [53, 57]. The melting procedure needs high-temperature conditions at 1300–1400°C [33, 58, 59]. Previously, after the oxide precursors via ball mill procedure, the blend is melted in a Pt-crucible, then quenched to 25 °C in order to fabricate an amorphous BG. A specific downside of this technique is having a high-temperature treatment that evaporates the volatile component P_2O_5 [44].

BGs are mostly materials based on silica with calcium and phosphate as two necessary components. A conventional BG is melt derived and has a composite consisting of 45% SiO_2, 24.5% CaO, 24.5% Na_2O, and 6% P_2O_5. In some studies, various compositions were synthesized by adding ingredients with various material and biocompatibility properties. Synthesis of melt-derived BG material not only is not complex but is appropriate for mass production also [33, 60, 61]. In addition, the melt quench procedure makes chemical heterogeneity of the synthesized composite with regard to crystallization or contamination during grinding, annealing, or quenching. The classical melt-quenching technique provides a more efficient and widely utilized procedure for oxide glasses [53].

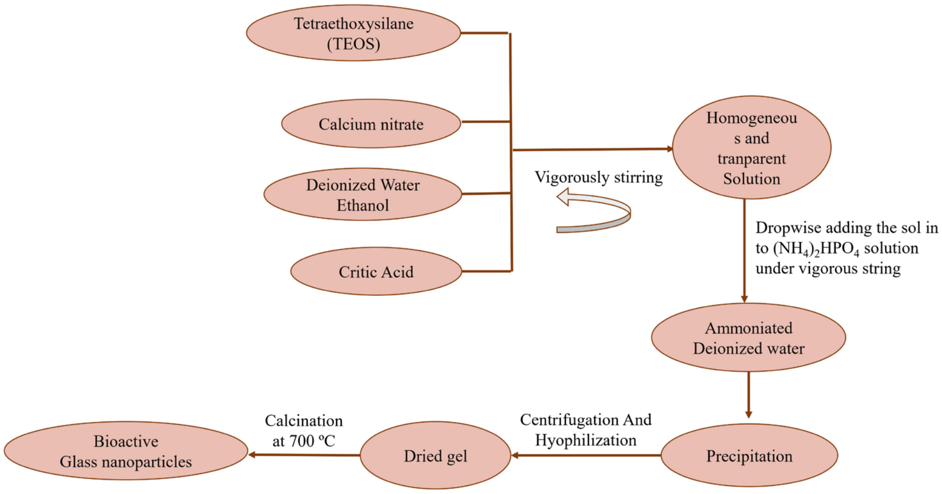

Fig. 2. The schematic for the sol-gel fabrication method of silicate BGN.

Melt-derived glasses not only have remarkable potential for taking excellent optical and physical properties but also show an effective AC conductivity range [47]. Some benefits of melt quench are desirable physical and optical characteristics and high AC conductivity. Although a few studies are accessible to the antibacterial investigation of melt-quench derived glasses, the considerable reports are based on the sol-gel derived BGs. For example, Tulyaganov et al. investigated the fabrication and characterization of the new bioactive glass-ceramics (GCs) containing alumina in the system of CaO-MgO-SiO_2 with Al_2O_3, CaF_2, Na_2O, P_2O_5, and K_2O additives. They applied compact sintering of glass powder and glass-melt quenching for the production of well-sintered and dense GCs. The results indicated that their fracture toughness (2.1–2.6 MPa $m^{0.5}$), microhardness (6.0–6.7 GPa), and elasticity modulus (27–34 GPa) are more compatible with human's dentine and jaw bone and the mechanical features of the prepared GCs were better than zirconia and titanium implant materials. The fabricated bioactive GCs were indicated using hydroxyapatite formation on their surface after they were immersed in simulated body fluid at the temperature of 37 °C [62]. Hmood et al. chemically modified BGs based on ICIE16 with the melt-quenching technique by water as a quenching medium. Also, they demonstrated that the sintering ability of advanced glasses is significantly associated with the suggested chemical additions. The BP1 glass which sintered at 20 K/min heating rate at 750 °C for 60 min had the highest density of 96 % [63]. Shahid et al. prepared a SiO_2–P_2O_5–CaO–SrO–Na_2O–CaF_2 BG via the melt quench method. The results revealed the fact that compressive and flexural strength is considerably higher in silylated BG composites. However, the strengths of both nonsilylated and silylated BG compositions and IG compositions were reduced when immersed [64]. Elalmis, et al. used the melt-quenching procedure for preparing biosilica and commercial silica-based BGs and applied them on the solid phase of composite putties which is produced by sodium alginate polymer as the liquid phase. The material characteristics of biosilica-based BG/alginate formulations synthesized by melt-quenching technique indicated the related features for bone tissue engineering applications [65].

2.2. Sol-gel

The sol-gel method is usually utilized for producing materials like metallic ions in the case of BGN and silicate tetrahedron from building blocks also this technique is a wet-chemistry method that mainly requires condensation and hydrolysis of stabilization, drying, and precursors. The features of materials like composition and morphology can be regulated by adjusting the parameters of the process. In the sol-gel fabrication of BGN, the most broadly applied precursor of silicate is tetraethyl orthosilicate (TEOS) while ethanol and/or water are applied as solvents [50]. Furthermore, the method is conducted at room temperature, avoids the evaporation of fugacious precursors including P_2O_5, and then achieves a superb purity and homogeneity of the product. However, it allows fabricating materials consisting of various inorganic-organic hybrid and oxides via more metal alkoxides (common precursor) and various additives like inorganic salts [66]. The sol-gel method has significantly been used owing to the restrictions mentioned. Because of its higher surface Si-OH groups, It's into greater functionalizing ability [67]. The sol-gel method can occur by basic or acidic methods that influence the resulting material characteristics. By altering the solvent pH, for instance, various morphologies of BGs can be fabricated. Precursors of metal ion can be introduced during the condensation and hydrolysis of TEOS or after the fabrication of SiO_2 nanoparticles [50]. BGs have been developed by adding lithium, silver, copper, zinc, magnesium, and strontium in bone tissue engineering fields. These ionic dissolution structures stimulate the response of the human body to biological characteristics including antibacterial activity features and osteoconduction [68]. Especially, the relatively low-temperature sol-gel method facilitates manufacturing the sophisticated BG structures like nanoparticles and porous scaffolds to form hybrid BGs as well as to combine growth factors and drugs [69].

The synthesis of biomedical sol-gel glasses mainly consists of 7 following reaction steps:

1. Mixture of the reagents at 25°C and formation of strong covalent bonds. During this step poly-condensation, reactions and hydrolysis are competitive and occur simultaneously, and it continues until complete solution homogenization under mild reaction conditions;
2. The sol casting into several shapes molds for investigation of the final product geometry. However, if the mixing container has a suitable shape and material, this step is not necessary;
3. Gelation, the formation of a 3D network, and a dramatic increase in viscosity. In addition, the variation of viscosity is strongly related directly to time and material can be drawn into fibers by the gelation;
4. Aging, with a decrease of the porosity of the material, the poly-condensation continues in this step, and the strength increases because of the matrix densification. This step avoids the drying phase and cracking so it is a fundamental step;

5. Drying, this step eliminates the liquid phase from the pores. The most important problem after the production of monoliths is the shrinkage and the cracking. These phenomena occur during this phase, and in most cases result in the material fracture;
6. Chemical stabilization or dehydration, in this step silanol bonds are removed from the pore network and make the chemically stable solid;
7. Gel densification by high-temperature thermal treatment used for the production of melt-derived glasses. In addition, by elimination of the pores, the levels of density are obtained which are comparable with quartz or fused silica [70]. The schematic diagram for the process of silicate BGN under sol-gel synthesis has been shown in Fig. 2.

On the other hand, specific biological features like blood vessel formation and wound healing enhancement, can be achieved by appropriately selecting chemical composition. Thus, the sol-gel method is ideal [44]. Fang et al. synthesized nano-bioactive glass by the sol-gel method. In their research, they developed mesoporous structures and applied Ca and P ions as additives. As a result, the BG microstructures had an approximate particle size of various hundred nm. The chemical compositions and phase structures are criteria for the feasible deposition of the biomimetic minerals after applying in the solution of simulated body fluid [51, 54, 71].

Leitune et al. prepared sol-gel particles without or with niobium addition (BAG or BAGNb, respectively). The results indicated that sol–gel-derived BGs developed enhanced cell viability and mineral deposition for experimental adhesives with growing phosphate amount and longitudinal μTBS contents for the A_{BAGNb} group. These outcomes offered that the capability of the investigated particles was desirable to be employed as bioactive fillers for dental adhesives [72]. Another study by Delpino et al. suggested a new branch of BGs which was sol-gel-derived ones consisting of holmium oxide, based on the system (100-x)($58SiO_2$-33CaO-$9P_2O_5$)-xHo_2O_3 (x = 1.25, 2.5 and 5 wt%). These results indicated that these glasses are desirable materials for brachytherapy applications because of their high cell viability, excellent bioactivity, and suitable dissolution behavior [73]. The results presented that the fabricated BG indicated promising biocompatibility and attractive bioactivity after in vitro experiments in cellular medium and simulated body fluid (SBF). Deliormanlı et al. synthesized electrospun nanofibers and sol–gel-based erbium (Er^{3+}), terbium (Tb^{3+}), and Er^{3+}: Tb^{3} co-doped BG powders. It resulted that Er^{3+} and Tb^{3+}-containing BGs can be desired candidates to use in bioimaging investigations (e.g., MRI imaging) and tissue engineering fields [74].

2.3. Gas-phase synthesis method (flame spray synthesis)

Flame spray fabrication paves the way for the addition of elements to complex materials like BGs to maintain nanoparticulate characteristics. Flame spray fabrication is a cost-effective and scalable process for the production of inorganic nanoparticles. In addition, this procedure ensures the distribution of narrow particle size further to the low product contamination risk. The flame spray synthesis method is one of the most effective techniques that is based on the gas phase. This technique also utilizes metalorganic precursors to generate nanoparticles at temperatures above 1000°C, where the metalorganic precursors are ignited in a flame [75, 76].

An advantage of the mentioned condition in comparison with other gas-phase processes is no further energy source needed for the precursor conversion like electrically heated walls, or lasers, plasma. In a tuned system, by utilizing oxygen over a nozzle, the liquid precursor is dispersed and therefore fabricates an ignited spray. The organic components of the liquid precursor are completely ignited and oxidization of the metal components is achieved to fabricate the nanoparticles. The fabrication of molecular nuclei from either chemical reactions or condensation and followed by growth via coalescence in regions with high-temperature in process duration is the fundamental principle of every gas-phase formation technique. The dynamic of the process is well found and can be controlled. Furthermore, the metal-organic salts are fully miscible among each other, tolerate humidity, and are remarkably stable in air. The nanoparticles that are mixed with oxides and even salts with great chemical homogeneity are produced by the process. As a consequence, the synthesis of various BGs has turned into via applying associated mixtures of fluorobenzene, tributyl phosphate, hexamethyldisiloxane, and 2-ethyl hexanoic acid salts of sodium and calcium for fluorine introduction. The rapid cooling, short residence times as well as the high-temperature atmosphere in the flame reactor leads to the formation of metastable polymorphs or phases directly after the generation of the particles. They are not easily available using conventional procedures. The fast quenching can retain the material's amorphous state depending on the composite. As a consequence of process properties and factors, the primary produced particles have spherical shapes with various agglomeration degrees [45, 77, 78].

As mentioned, the benefits of flame spray fabrication are associated with the confirmed scalability of the method, the facile introduction of dopants, and the favorite availability of various nanoparticle compositions. Therefore, it has been interesting for numerous researchers. For instance, Tauböck et al. studied the impact of particle size of BG 45S5 on physical and chemical composite features. The experimental compositions were synthesized by melt-quench technique and via synthesis of flame spray. The results indicated that downsizing BG particles to nano-size modified the alkalizing potential of experimental compositions with a positive influence on their basic characteristics [42].

2.4. Microwave synthesis

Microwave manufacturing techniques can furnish the yield with superior purity in much shorter time and control the fabrication process. In the microwave-assisted method, the powders can be formed by applying for an effective and modified heat transfer all over the volume [79]. The microwave-assisted technique is widely used for nanomaterial synthesis. The vessel is heated and heat is transferred via convection in conventional heating. However, energy transfers more homogeneously and rapidly in the microwave [56]. The microwave sintering advantages contain enhanced sintered-body density and decreased grain sizes at lower temperatures of sintering as well as significantly faster heating rates over conventional strategies. Furthermore, microwave sintering provides mechanical characteristics owing to finer microstructures obtained at equivalent sintering temperatures to conventional resistance heating [80, 81]. Khalid et al synthesized E-glass fiber bioactive by microwave technique. The images of Scanning Electron Microscopic (SEM) approved the homogenous adhesion of nano-hydroxyapatite spherical particles whole the fibers. Cell viability with mesenchymal stem cells indicated adhesion, proliferation, and growth [82]. Furthermore, In order to improve the biological activity of hydroxyapatite (HA), a multi-substituted HA (SHA) nanopowder with the chemical composite of $Ca_{9.5}Mg_{0.25}Sr_{0.25}(PO_4)_{5.5}(SiO_4)_{0.5}(OH)_{1.2}F_{0.8}$ was fabricated by the microwave-assisted technique. The results indicated that the release of the replaced ions not only had excellent influence on the cell attachment and cell viability, but also increased the activity of alkaline phosphatase of MG63 osteoblast such as cells in the group of SHA, as in comparison with the control groups and HA. Also, the results presented that the simultaneous replacement of F, Sr, Mg, and Si in HA nanoparticles could desirably enhance cell differentiation and proliferation as well as bioactivity. This new composite of HA could be, thus, well utilized for bone tissue engineering, implant coating, and other orthopedic applications [83].

3. Effect of ion substitution on bioactive glass

BG has been developed via a combination of biologically active elements like zinc, copper, magnesium, and strontium to impart special biological applications and also to develop therapeutic behavior. Zn^{2+} is not only an important element for differentiation, proliferation, and cell growth, but possesses a significant role in enzyme production, growth factors, and DNA replication. Furthermore, Zn^{2+} reveals stimulatory influences in the formation of bone and prevents bone mass, in vitro and in vivo. Indeed, the slight release of Zn combined with an implant material develops bone formation in the implant and advances recovery of the patient; Cu^{2+} plays an important role in healing and formation of bone, and develops the process of angiogenesis; Mg^{2+} is related to calcified tissue mineralizations, osteoblast proliferation stimulating; hence, Mg^{2+} has usefully applied bone regeneration of implants; While reduction of osteoclast activity, Sr^{2+} has been presented to stimulate bone fabrication and develop the replication of preosteoblastic cells [10].

Zn is a desired antimicrobial factor and combines with BG composites to the reduction of infections and improvement of healing after surgeries. Actually, because of difficulties in the fabrication of antibiotics, the preventing of infections after surgery becomes a significant challenge. Duration of treatment, drug concentrations, and physiological barriers form the significant reasons for failure; a higher concentration of drugs is provided by local drugs delivery systems at the considered place than antibiotics given or taken via injection. Silicate glasses including Zn, Mg, and Sr possess the potential to release ions at the place to prevent post-surgical infection [10, 84]. Kalkura et al. reported calcination without applying mould, polymers, and other additives and synthesis of mesoporous (45S5) BGs doped with very slight (≤0.2%) strontium ion using sol-gel method. The total outcomes robustly indicated the very slight doping of Sr ions (≤0.2%) in BG for the first time, tuning cell proliferation, drug release, and the mechanical and surface characteristics made them desirable for applications of multifunctional biomedical fields [85].

Additionally, a brand new porous microstructure of Sr-substituted BG microspheres was synthesized by Guo et al. using an electro-spraying method integrated into the inversion of phase. The outcomes offered that the Sr substituted ESBG microspheres can deliver a steady supply of drugs and therapeutic ions in patients of bone implantation [86]. Moreover, BG of SiO_2-P_2O_5-CaO with various elements of Mg and Sr were fabricated by the sol-gel technique and immersed in simulated body fluid (SBF) for a period of time to devise their biocompatibility. It was found that the mechanical characteristics of the BG could be modified via the addition of SrO and MgO amounts. On the other hand, the Sr-doped BG composition consisted of 5 wt % SrO showed developed biocompatibility and bioactivity [53]. Accordingly, the ion-doped BG dissolution has been led to the controllable release of metal ions with critical amounts indicating in the desirable aspects advantageous anti-inflammatory impacts (Zn-BG) or growth of osteoblast activity (Sr-BG). On the other hand, more citable investigations are required to approve the therapeutic impacts of single biologically active metal ions released as dissolution samples from bioactive glasses. Hence, the exact study of the outcomes is prevented via the point that the biological function of the material relies on whether cells are directly seeded on the material or are used to liquid extracts including the dissolution samples and it is used as an ionic extract, particle suspension, porous scaffolds, or dense substrate. Furthermore, the addition of considerable values of metal oxides to the glass network leads to the total changed dissolution status of the glass, making it impossible to compare the outcomes to those on unimproved control glass [87].

Table 1.
The substitution effects of some selected ions on the BG for many applications.

Ion	The fabrication method	Application	Influence	Ref
Strontium/ zirconium	Sol-gel	Bone regeneration	Delayed hydroxyapatite (HA) formation by incorporation of Sr in content range of 6 to 9 (mol.%) compared to 3 and 6 (mol.%). Weakening of network connection via Sr incorporation. Enhanced cell proliferation by 6 (mol.%) Sr incorporation. Weakened cell proliferation by 12 (mol.%) Sr. ALP activity promotion by Sr contents of 3, 6, and 9 (mol.%). 90% antibacterial activity with 5 (mol.%) Zr and 6 (mol.%) Sr. Improved growth of nuclei and cytoskeleton by incorporation of 6 (mol.%) Sr.	[88]
Strontium	Sol-gel	Bone regeneration	Strongest inhibitory effect of Sr-SBG on osteoclast differentiation	[89]
Magnesium or zinc	Melt-quench	Therapeutic concentrations	Higher density glass structure by Mg or Zn incorporation. Aqueous environment stability in the high concentration of Zn	[90]
Magnesium or zinc	Melt-quench route	BG 45S5	Improved sintering of BG 45S5 by substitution of Mg/Zn.	[91]
Zinc/Zirconium	Sol-gel	Bone regeneration Antibacterial agents	Augmented osteoblast-like proliferation and osteogenic response, and higher microbial resistivity by Zr/Zn incorporation.	[92]
Copper	Sol-gel	Antibacterial agents	Prohibition of post-surgical infections and capability for hard tissue regeneration by substitution of Cu in bio-glass.	[93]
Argentum (silver)	Sol-gel	Antibacterial agents	Ag-incorporated BG with the chemical composition of 60SiO2–30CaO–4P2O5–5Li2O–1Ag2O was introduced as an optimal novel co-doped BG in biomedical applications due to causing higher differentiation and proliferation of MC3T3-E1 cells and more increase in ALP activity and bactericidal efficiency.	[94]
Copper	Sol-gel	Bone regeneration	The potential application of copper-incorporated mesoporous bioactive glass (MBG) powder for bone regeneration (bioactivity), and microbial infection prevention at the implantation site, thus promoting tissue healing.	[95]

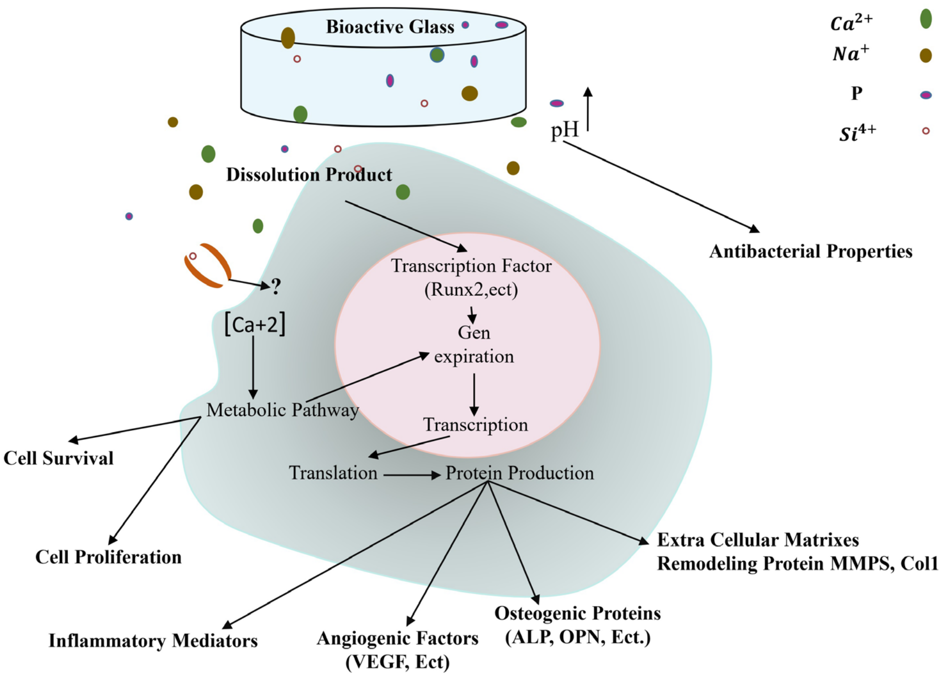

Fig. 3. Biological properties of a BG.

4. Applications of bioactive glass

4.1. Bone grafting

In modern medicine, after blood transfusion, bone grafting is the most conducted transplanting of tissue in the US. Annually two million bone grafting is conducted [96]. On the other hand, BGs have been successfully employed as substitutions for bone. Moreover, BGs are the first synthetic materials that possess the ability to attach to the bone due to the formation of a biologically active layer of hydroxycarbonate apatite (HCA) over the exposed surface. This layer resembles the bone's mineral phase in terms of structure and chemistry. The comparison of two conventional biomaterials, beta-tricalcium phosphate (β-TCP) and 45S5 BG was shown in recent research. As presented by new bone areas and elevated bone mineral density (BMD), the fabricated pH-neutral bioactive glass (PSC) noticeably enhanced BMSCs' proliferation, mineralization, and migration in addition to their angiogenic and osteogenic differentiation. PSC displayed better performance in the stimulation of bone regeneration than both β-TCP and 45S5 in vivo. PSC also notably augmented the formation of new blood vessels in comparison with the ones in control groups [92, 97, 98]. Although bioactive glasses are naturally brittle, they are undesirable for load-bearing components. As a result, reinforce 3D porous scaffolds via changing weight percent of carbon nanotubes (CNTs) have been fabricated by physical blending and method of polymer foam replication. In comparison to pure 13-93B1 bioactive glasses, adding 0.2 weight percent of CNT led to a major enhance in compressive strength from 1.80 MPa to 5.84 MPa (a 224% enhancement) and elastic modulus from 102 MPa to 269.4 MPa (a 164% enhancement), respectively [99]. Also, the CNT-reinforced scaffolds were deposited with the polymer polycaprolactone (PCL) via dip-coating technique for the modification of their characteristics further to sealing the micro cracks. The polymer coating and CNT reinforcement led to modification in the compressive strength of the additively fabricated scaffolds by 98% compared to scaffolds of pure bioactive glass [100].

Moreover, PSC induced angiogenic and osteogenic differentiation of BMSCs via the PI3K/Akt/HIF-1α route. This synergistic influence of the PI3K/Akt/HIF-1α route on angiogenic and osteogenic differentiation of BMSCs offered that biomedical materials may enhance the novel bone fabrication by multiple signal routes, therefore shedding light on the addition advancement of materials with higher function [8]. In addition, BAG exhibited osteoinductive properties, like 45S5 BG which promotes osteoblastic activity due to the release of its ions and apatite crystallization at its surface. Surprisingly, this infusion exceeds that of hydroxyapatite. The dissolution products like P, Ca, Si, and Na, stimulate bone formation (Fig. 3). In vivo studies demonstrated that 45S5 BG capacity for bone repairing is more efficient in comparison with other kinds of bioactive ceramics [6].

Although the various applications of BGs (especially 45S5 BGVR) in clinical programs have shown that these glasses possess favorable healing capability, the fast dissolution rate is one of their major problems. This problem mainly is because of their great alkali content (>20 mol %) and it causes high reactivity in physiological environments and fast degradation paces that may not be suitable for the new growth of bone, compromising bone regeneration in critical defects [101]. A total of maxillary sinuses with Biogran via autogenous bone graft (group 1) and 12 mixed with autogenous bone graft (group 2) has been reported by Menezes et al. They realized that if the BG was mixed with autogenous bone (1:1) it was safely capable for bone substitute applications as the maxillary sinus lift [102]. In another study, Baheiraei e al. combined different concentrations of strontium-delivering glasses with the fabricated composites containing gelatin. As a result, they indicated that Sr-containing BGs could exert beneficial effects on bone tissue engineering [103].

4.2. Bone regeneration

Over the past decade, bone regeneration studies have proved that insufficient or delayed vascularization is a major challenge for a successful translation of regenerative medical devices into clinical products. Promoting blood vessel infiltration into the scaffolds is important to achieve and maintain the long-term function and viability of vascularized bone. Restrictions on oxygen or nutrient diffusion, mostly result in the confinement of viable cells to superficial or near the outer layers of the tissue constructs. Thus, bone formation in the central regions of the scaffold

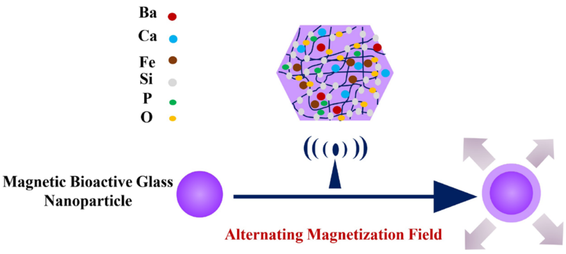

Fig. 4. Schematic illustration of MBGs that are prepared for cancer hyperthermia therapy.

is limited. In bone regeneration, this can be bone-bonding and/or stimulation of bone cells to produce more bone. In addition, the influence of combining villa quite / nano glass with FGF-18 compared to nHAP / FGF-18 (commercial bioceramics) was reviewed by Amirthalingam et al. Chitin PLGA was used to regenerate skull and facial bones when delivered via hydrogel. Nano gels (nBG) were in the amorphous phase, which is desirable for bioactivity and prevention of bioactivity. The modulus of storage for CGnBG (nBG composite hydrogel (10% by weight CG)) increased compared to CG (composite hydrogel) and achieved higher specific surface area (larger nBGs) and higher nBG concentration. They also led to the absorption of more CGnBG protein. Thus, slower FGF-18 release was needed for regeneration of bone tissue, which CGnBG provided the more stable release of FGF-18 than other samples [104]. A multi-scale porous scaffold was created by Cerezo et al. whereby macro, micro, and mesoporosity were created using three-dimensional printing, porosity washing, and merging of porous meso-BG particles. The resulting scaffold showed a highly interconnected porosity that is inherently employed in the additive production method. It is proper for the facilitation of the new blood vessels and bone formation [105]. 3D structural characteristics including tortuosity, interconnectivity, and pore size of scaffold have a significant role in bone tissue regeneration. Dixit et al. reported the structural analysis of scaffold bioactive glass using imaging of micro-computed tomography (ICT). Images of ICT were filtered and binarized to achieve 3D scaffold reconstruction. The fast march technique was used on the 3D reconstructed scaffold to calculate tortuosity [106]. Simultaneously, methods of additive manufacturing (AM) have been interested in many researchers due to their ability of manufacturing patient-specific and complex scaffolds. Hence, borosilicate bioactive glass (BG-B30) has been applied to manufacture the scaffolds by devices of an extrusion-based AM in a recent study. They used pluronic F-127 as an ink carrier, indicating desirable shear thinning behavior for manufacturing. The reinforced scaffold of pure BG-B30 was further with functionalized multiwalled carbon nanotube (MWCNT-COOH) for enhancement of its compressive strength and reduction of its brittleness and had a compressive strength of 23.30 MPa [107].

In addition, an optimal bone and angiogenesis-inducing scaffold were fabricated by Eslaminejad et al. using the fusion of strontium and BG in gelatin / nano-hydroxyapatite (G / nHAp). It was seeded with mesenchymal stem cells. They created bone marrow to strengthen bone marrow mesenchymal stem cells. The results exhibited that the combined nHAp, BG, and Sr could improve bone regeneration synergy. Moreover, they showed that BMSCs had the potential to significantly increase the ability of bone regeneration for osteoinductive scaffolds [25]. The in vivo and in vitro behaviors of the heat-sensitive composite of hydrogels based on BG polymers /nanoparticles were described by Moreira et al. The developed injectable composite hydrogels were suggested by them which have properties that make them desirable candidates for use as temporary injectable matrices for application of regeneration of bone [108].

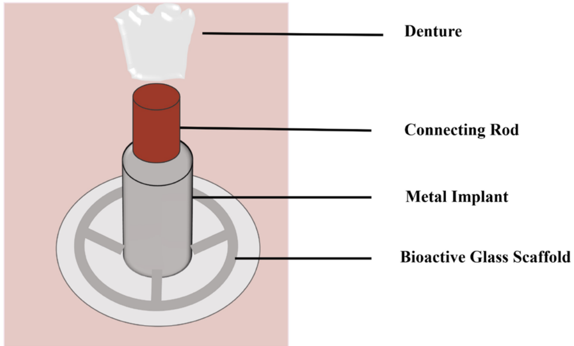

Fig. 5. Schematic of the scaffold dental implant system (SDIS): a connecting rod joined the central hole of the metal implant and the denture.

4.3. Drug delivery

The therapeutic ions inclusion in the glass structure and their release after dissolution BG is usually insufficient to obtain the multifunctional characteristics needed for stimulating the excellent activities or tissue responses (including antibacterial performance and suitable vascularity). In order to tackle this problem, Yan et al. [109] and afterward, López Noriega et al, [110] introduced MBGs. This BG type is the most recent sol-gel glass evolution. In this type of BG, in the wet synthesis of glass, a surfactant is included as a structure guiding agent. Moreover, it enables them to obtain a glass that possesses a structure that is very regular mesoporous (for example, hexagonal symmetry-based nanochannels arranged, pore diameters from several to several tens of nanometers) [111]. For several therapeutic purposes, mesoporous MBGs have loaded with various drugs including antibiotics (eg, tetracycline), growth factors [e.g., vascular endothelial growth factor (VEGF)], and anticancer agents (such as doxorubicin). As mentioned, the drug delivery method is controlled by several physical factors as well as chemical factors, such as surface volume, area, and pore diameter, in addition to charge and surface performance. MBGs through various chemical interactions have successfully loaded on various synthetic and natural drug biomolecules including anti-cancer agents, growth factors, and antibiotics. The main interactions happen between the functional alkoxysilanes of MBGs and the therapeutic agents' organic groups (R). Aside from these mesoporous materials advantages that were mentioned, also there have been challenges in using them as systems of drug delivery (DDS). The hydroxyapatite layer formation on MBGs based on silicate is one of the major challenges that interfere release of the therapeutic agent. In addition, another problem is that by applying heat during glass firing loaded biomolecules degrade and denature. The organic solvents used during the glasses preparation are also recognized as an undesirable factor that causes the denaturation of biomolecules (for example, proteins) [112].

In addition, BGs are increasingly employed as magnetic materials in the hyperthermia strategy. Moreover, some of their subdivisions, mesoporous bioactive glasses (MBGs), have recently been used as magnetic materials as well as delivery systems for improved bone cancer therapy. It has been shown that after exposure to an external magnetic field of alternating, magnetic BGs can function like an anti-tumor agent through an extraordinary thermal effect. (Fig. 4) [113]. Hence, different MBG types, such as 3D scaffolds and granular particles, can be used to treat cancer. Regarding the resulted of laboratory studies, MBGs seem to be promising in therapeutic strategies for fighting cancer. However, MBGs applications in this field of study remain in its infancy. Thus, further research is needed to reveal all the cons and pros of this new approach proposed.

By increasing copper incorporation in BAG increase by Balakmar et al., the results indicated an improvement in anti-inflammatory agents like ibuprofen (IBU) and acetaminophen (ACE) release. Their

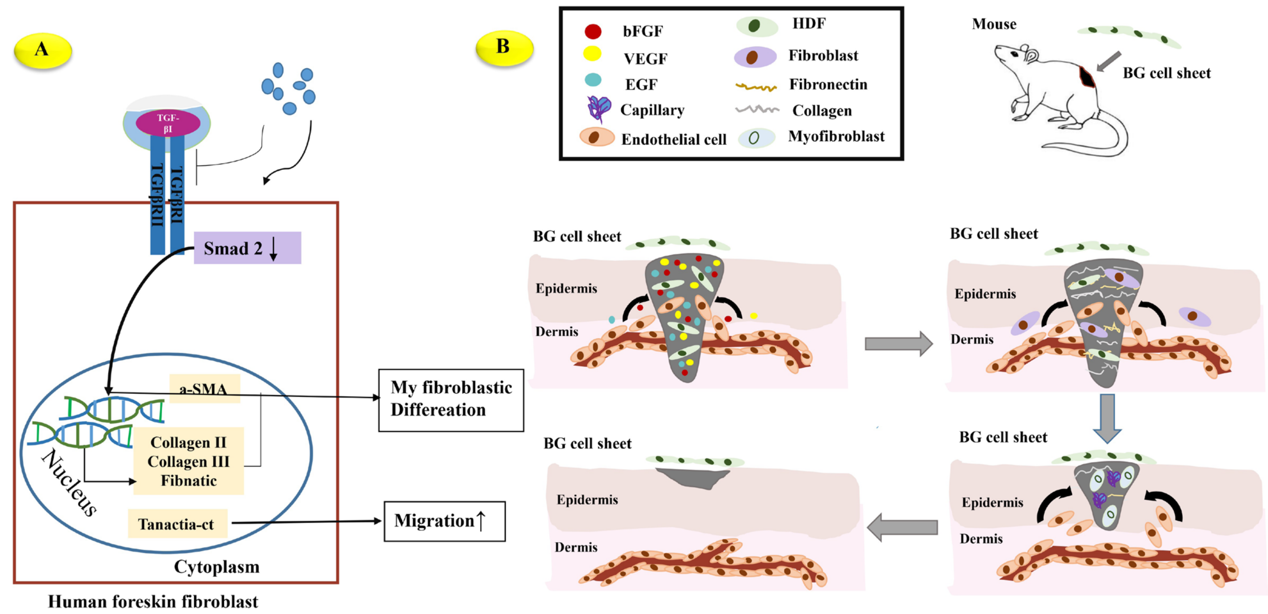

Fig. 6. Proposed mechanisms of BGs based on silicate in wound healing. A) The possible BGs mechanism in wound healing, in vitro B) The BGs' mechanism in activating skin fibroblast cell membrane transplantation to improve wound healing, in vivo.

study showed that up to a certain proportion of copper integration in the BAG network, potentially increases biomineralization and converts the morphology to a minimum with mesoporous nature [114]. The biological activity and loading efficiency of the fiber drug were investigated by Amini et al. No initial release of cisplatin from BGs/Cisplatin and MBGs /Cisplatin nanofibers loaded with Cs-g-PCL / MBGs was observed, and the release rate of cisplatin was accelerated at pH 5.5 and 43 °C compared to physiological conditions. The effect of apoptosis/necrosis showed that 100 µg/mL nanofibers are optimal for killing MG-63 cell types. The focus of prospective researches may be on the use of nanofibers as devices compatible with being implanted alongside bone tumors for the treatment of bone cancers in vivo. In addition, MBGNPs doped with cerium and gallium by a sol-gel assay using microemulsion in a SiO2-CaO binary system by Cortoldo et al. were prepared. The results of MB and Ce doped MBGNPs make them useful for multipurpose applications such as drug carriers or bioactive fillers for bone tissue engineering applications [115].

4.4. Dental implant coatings

BGs can be used as bone substitutes. However, the mechanical strength of BGs is not desirable like that of human cortical bone. Hence, a broad range of precipitated-glasses crystalline phases has been prepared, known as bioactive glass-ceramics. Cervical, which precipitates apatite in Na_2O-K_2O-MgO-CaO-SiO_2-P_2O_5 glass, AW glass-ceramic (widely used in clinical practices), which apatite and wollastonite precipitate in MgO-CaO glass -SiO_2-P_2O_5, are a few to name. Other GCs to mention are the precipitations of apatite and phlogopite in Na_2O – MgO – CaO – Al_2O_3 – SiO_2 – P_2O_5 – F glass and the precipitations of apatite and wollastonite in Na_2O – K_2O – MgO – CaO – SiO_2 – P_2O_5 – CaF_2 glass, which is known as Bioverit and Implants, respectively. Table 2 shows the most ceramic glass and BG as a material in dentistry [116]. The function of a material without damaging the surrounded tissues determines whether it's suitable for dental applications. To name, plasma electrolytic oxidation (PEO) has been introduced by Costa et al. [16] as a new strategy for the bioactive synthesis of coatings on titanium (Ti) that are glass-based (PEO-BG). PEO-BG increased the tribological and mechanical traits of Ti by improving its corrosion resistance. Additionally, PEO-BG affected polymicrobial biofilms positively by decreasing pathogenic bacteria that are responsible for infections in biofilm. Moreover, PEO-BG exhibited higher uptake of proteins of blood plasma without any cytotoxic activity on human cells. Therefore, they can be ideal and biocompatible candidates for biomedical implants. In addition, cementum possesses a structure similar to bone tissues however, it's less hard than dentine (<0.6 GPa). Thus, it does not contribute to the mechanical strength of natural teeth. Cementum's function is only restricted to tooth preservation in the alveolar and root coverage. Therefore, exhibiting mechanical characteristics similar to the natural tooth is crucial for a candidate material for the dental implant. It's important to note that those mechanical properties should not exceed jaw bone's mechanical properties [51]. In the system of CaO-MgO-SiO_2, GCs contain diopside ($CaMgSi_2O_6$) and wollastonite ($CaSiO_3$) as main crystalline phases. GCs display fascinating characteristics for material development for biomedical purposes. Recently, novel compositions of GCs in the system CaO-MgO-SiO_2 were reported by Dimitriadis et al. These compositions contained different ratios of Na_2O/K_2O, CaF_2, and P_2O_5 and have shown great mechanical characteristics and bioactivity which are close to those of the jaw bone. To enhance the in vitro performance as well as the compatibility of properties of physical-mechanical with those of bones of a human, bioactive glasses and GCs, in these systems, usually undergo modifications by adding special oxides like B_2O_3, Al_2O_3, Fe_2O_3 ZrO_2, Li_2O, and K_2O [53].

4.5. Antibacterial agents

Infections that are induced by bacteria have been found the main clinical obstacle for successful tissue regeneration/repair. For example, the risk of bacterial attachment and colonization in bone implants may lead to failure implantation or long-term recovery. Many efforts have been made to eliminate or decrease the risk of bacteria-induced infections. The primary solution to this challenge is the use of antibiotics. Nevertheless, the antibacterial activity of antibiotics can be weakened because of the continuous evolution of bacteria that results in antibiotic resistance. Alternatively, clinical applications of intrinsically antibacterial materials may prevent the infection risk without developing bacterial resistance. Conventional compositions of BG, for example, S53P4 and 45S5 BGs, have exhibited antibacterial activity by enhancing the local pH during the dissolution of glass. Nevertheless, toxicity towards mammalian cells may be caused as a result of activities of the said type [117-120].

New compositions that have shown remarkable and selective antibacterial effects are interesting in the field of tissue regeneration. Among the metal ions that have long been applied as antibacterial agents, Ag has shown a wide-spectrum bactericidal properties. Ag application was shown to be a practical strategy to increase the BGs' antibacterial activity [121]. A novel BG called Huaxi bioactive glass-ceramic (HX-BGC) was developed by Lu et al. in 2020. The antibacterial properties of HX-BGC were investigated thoroughly. It was reported that acid production, as well as the growth of the cariogenic bacteria, were effectively inhibited by HX-BGC [9, 122-124]. Table 3. presents some listed compositions of bioactive glass with antibacterial agents.

4.6. Soft tissue engineering

BGs are a classic example of third-generation biomaterials and have displayed remarkable success in repairing, regenerating, and replacing damaged tissue owing to their capability to release therapeutic ions to form a layer of appetite when they are dissolved in physiological fluids. Since the first BG development, a wide range of BGs has been developed as a result of various compositions of glass and various preparation strategies. Some are highly applicable for tissue engineering, including both soft and hard tissues. Recent advances in the progress of borate bioactive glass (BBG) has developed the repertoire of bioactive glasses [142, 143]. The developments of BBG in expanding cell growth and its full biodegradation are especially effective for the repair of soft tissue [144, 145]. Zhao et al. fabricated the microfibers of BBG that can incense angiogenesis and develop skin defect repair [146]. Furthermore, Saatchi et al. indicated that by increasing the (w/w) ratio of Ce-BG / CH up to 40% in scaffolds, cytocompatibility of the scaffolds was remarkably improved. It was found that enhancing the 8Ce-BG/CH weight ratio up to 40 (wt.%) in the system of the scaffold was significantly beneficial for applications of soft tissue engineering [3].

Various physicochemical characteristics have been observed in the three kinds of BG. Furthermore, the cellular response after being implanted in the human body is considerably influenced by various types of bulk and surface features that can be assigned to various BG classes [147].

Surface topography, wettability, hydrophilicity, and surface area are primary parameters that regulate the interactions of biomaterial with cells and the biomaterials which control the long-term performance of the biomaterial [148]. For example, sol-gel-derived BG-AuNPs composites with Vaseline at 6, 12, and 18 wt% and BGs were combined by Sorin Marza et al. to assess the skin's repair response. The results of their study showed that ointment with 18% BG-AuNPs-Vaseline is an excellent candidate to be applied for wound healing. Additionally, the compatibility of PGS / PCL polymers for the fabrication of the composite fibers incorporated with particles of BG was investigated by Loginina et al. The achieved results from early biological experiments for the potential application of mats fabricated for soft tissue-engineered were promising [149].

Recently, reported results from an in vitro study exhibited that when fibroblasts were directly exposed to silicate-BG derived from sol-gel, TGF-b signaling, as well as its downstream Smad2 molecule, were down-regulated by 90S [(90) SiO_2- (6) CaO- (4) P_2O_5 (mol%)]. The results suggested that BGs may play a role in the TGF-b pathway modulation (Fig. 6a). Moreover, the 90S assisted the migration, proliferation, expression, and regulation of alpha-smooth muscle actin (α-SMA), fibronectin, and type I and III collagen. Thus, it inhibited the trans-differentiation to myofibroblast. The response of fibroblasts was significantly affected by Si^{4+} ions. Nevertheless, it is noteworthy that the regulation of collagen I and III is in contradiction with previous findings of the role of Si^{4+} ions in stimulating the formation of type I collagen in mineral tissues [150].

Yu et al. developed and reported the fibroblast-derived sheets and graft composite BGs based on silicate for the skin. The products of ionic dissolution were found to stimulate the fibroblasts for secretion of necessary growth factors for processes of healing and vascularization (Fig. 6b). Considerable in vivo newly formed blood vessels and wound closure were observed. Interestingly, type I collagen and α-SMA expression in cultured fibroblasts in the presence of the products of ionic dissolution of glass, were initially up-regulated on the third day and then down regulated on the seventh day. These findings indicated that modulation of TGF-β signaling's gene expression by ions may increase wound healing [151].

5. Challenges and Future Aspects

Accordingly, the ion-doped BG dissolution has been led to the controllable release of metal ions with critical amounts indicating in the desirable aspects advantageous anti-inflammatory impacts (Zn-BG) or growth of osteoblast activity (Sr-BG). On the other hand, more citable

Table 2.
The most popular BGs and CGs (wt%) in dental material.

	KGy213 ceravital	KGS ceravital	KGC ceravital	55S4.3 BG	52S4.6 BG	40S5B5 BG	45S5.4F BG	45S5F BG	45S5 BG
SiO_2	38	46	46.2	55	52	40	45	45	45
P_2O_5	-	-	-	6	6	6	6	6	6
CaO	31	33	20.2	19.5	21	24.5	14.7	12.25	24.5
$Ca(PO_3)_2$	13.5	16	25.2	-	-	-	-	-	-
CaF_2	-	-	-	-	-	-	9.8	12.25	-
MgO	-	-	2.9	-	-	-	-	-	-
MgF_2	-	-	-	-	-	-	-	-	-
Na_2O	4	5	4.8	19.5	21	24.5	24.5	24.5	24.5
K_2O	-	-	0.4	-	-	-	-	-	-
Al_2O_3	-	7	-	-	-	-	-	-	-
B_2O_3	-	-	-	-	-	5	-	-	-
Ta_2O_5/TiO_2	-	6.5	-	-	-	-	-	-	-
Structure	-	Glass-ceramic	Glass-ceramic	-	Glass	Glass	Glass	Glass	Glass

Table 3.
Some listed compositions of bioactive glass with antibacterial agents.

Active factor	Glass system	Organisms		ref
		Gram (+)	Gram (-)	
Ag^+	SiO_2-CaO-P_2O_5-Ag_2O	-	E. coli	[125]
		S. aureus	P. aeruginosa	[126]
		S. aureus	E. coli	[127]
	P_2O_5-CaO-Na_2O-Ag_2O	S. aureus	E. coli	[128]
	B_2O_3-Na_2O-P_2O_5-Ag_2O	Listeria monocytogenes	-	[129, 130]
	Ag_2O-B_2O_3-SiO_2-CaO	S. aureus	E. coli	[130, 131]
	SiO_2-CaO-P_2O_5-Al_2O_3-Na_2O-K_2O-Ag_2O	E. faecalis	E. coli	[132]
	45S5 bioglass	sanguis, S. mutans, A. viscosus and E. faecalis	E. coli, P. aeruginosa, Actinobacillus actinomycetemcomitans, P. gingivalis, Fusobacterium nucleatum	[133, 134]
[ions] pH	58 S and 63 S bioglass	S. aureus	E. coli, P. aeruginosa, Salmonella typhi	[135]
	$S_{53}P_4$	S. epidermidis, E. faecalis	Acinetobacter spp., Haemophilus influenza, Enterobacter aerogenes, M. catarrhalis, E. coli, P. aeruginosa	[136-138]
[Ca^{2+}]; pH	SiO_2-CaO-Na_2O-K_2O-P_2O_5/MgO	S. aureus	–	[139]
[Sr^{2+}]	SiO-SrO-CaF_2-MgO	S. aureus	–	[140]
pH	CaO-SiO_2	S. aureus	E. coli	[131]
Si^{4+}; pH	$S_{53}P_4$	–	E. coli	[141]

investigations are required to approve the therapeutic impacts of single biologically active metal ions released as dissolution samples from bioactive glasses. Hence, the exact study of the outcomes is prevented via the point that the biological function of the material relies on whether cells are directly seeded on the material or are used to liquid extracts including the dissolution samples and it is used as ionic extract, particle suspension, porous scaffolds, or dense substrate. Furthermore, the addition of considerable values of metal oxides to the glass network leads to the total changed dissolution status of the glass, making it impossible to compare the outcomes to those on unimproved control glass. Additionally, fabrication of bioactive composites should be evaluated in order to toxicity risk, owning lower element release rather than their biologically safe levels, render no or slight cytotoxicity. Although the various applications of BGs (especially 45S5 BGVR) in clinical programs have shown that these glasses possess favorable healing capability, the fast dissolution rate is one of their major problems. This problem mainly is because of their great alkali content (>20 mol %) and it causes high reactivity in physiological environments and fast degradation paces that may not be suitable for the new growth of bone, compromising bone regeneration in critical defects [101].

The development of new or improved bone graft substitutes is an important area of biomedical research. For example, there is interest in the use of 3-dimensional printing to replicate bony architecture and to deliver antibiotics or therapeutic agents in the settings of infection or oncological tumor extirpation. Various techniques have been employed including the use of ceramic- and mineral-based composites. Furthermore, there have been attempts to incorporate osteogenic cells and growth factors into these constructs to treat bone deficits in the settings of compromised vascularity, nonunion, and prior irradiation. As described previously, the particle size and porosity of a BGS influences graft efficacy and new bone ingrowth. Recent studies that investigate the replication of the ultrastructure of bone are proving effective: Tae Young et al have described the use of a polysaccharide HA-fucoidan nanocomposite in a rabbit bone defect model that resembles bone ultrastructure and demonstrates that this induces fibroblast growth factor-2, collagen formation, and angiogenesis. Another fascinating area of interest is the use of silk from the domesticated silkworm Bombyx mori as a bio-scaffold. Silk has been shown to be effective in the reconstruction of mouse calvarial defects by Meinel et al, and Pina et al have shown some success when a silk scaffold is used as the carrier of ionic CP for bone regeneration [152].

Furthermore, over the past decade, bone regeneration studies have proved that insufficient or delayed vascularization is a major challenge for a successful translation of regenerative medical devices into clinical products. Promoting blood vessel infiltration into the scaffolds is important to achieve and maintain the long-term function and viability of vascularized bone. Restrictions on oxygen or nutrient diffusion, mostly result in the confinement of viable cells to superficial or near the outer layers of the tissue constructs. Thus, bone formation in the central regions of the scaffold is limited that can be considered for future investigations to solve these challenges. Aside from mesoporous materials advantages that were mentioned, also there have been challenges in using them as systems of drug delivery. The hydroxyapatite layer formation on MBGs based on silicate is one of the major challenges that interfere release of the therapeutic agent. In addition, another problem is that by applying heat during glass firing loaded biomolecules degrade and denature. The organic solvents used during the glasses preparation are also recognized as an undesirable factor that causes the denaturation of biomolecules (like proteins).

We recommend future studies on dentin remineralization using bioactive glass to give importance to the following key points as a means of ensuring a full comparison of results.

- Basic characteristics of the bioactive glass such as composition and particle size.
- Confirmation of apatite in dentin by using one of the following analytical techniques: XRD; FTIR; TEM combined with SAED pattern; Raman spectroscopy. A combination of 2 methods for confirmation, as employed by Wang et al., and quantification of the mineral content will strengthen the results.
- Most importantly mechanical properties of the dentin after remineralization treatment such as flexural strength, Young's modulus, and hardness by techniques such as atomic force microscopy (AFM) or 3-point bending test are crucial [153]. Furthermore, tuning the mechanical properties of BGs should not exceed jaw bone's mechanical properties and would be considered a novel topic for future studies.

Although the considerable reports are based on the sol-gel derived BGs, a few studies are accessible to the antibacterial investigation of melt-quench derived glasses; it is needed to further studies. The primary solution to the challenge of bacteria-induced infections is the use of antibiotics. Nevertheless, the antibacterial activity of antibiotics can be weakened because of the continuous evolution of bacteria that results in antibiotic resistance. Alternatively, clinical applications of intrinsically antibacterial materials may prevent the infection risk without developing bacterial resistance. Conventional compositions of BG, for example, S53P4 and 45S5 BGs, have exhibited antibacterial activity by enhancing the local pH during the dissolution of glass. Nevertheless, toxicity towards mammalian cells may be caused as a result of activities of the said type

6. Conclusions

Bioactive glass has been used for tissue engineering applications of bone healing. They can be considered as promising materials for making bone regenerating scaffolds, due to the adaptable properties which make them suitable for their composition. Many trace elements can also be incorporated into the glass mesh to achieve promising properties that have a positive effect on associated angiogenesis and /or bone regeneration. Several kinds of literature have been published to this date on BGs, proving their outstanding versatility, which is owed to the flexibility of their composition. By changing the composition of glass other properties will be affected as well (e.g., bioactivity). This can be taken into consideration and advantage because the careful and wise design of the composition of glass enables us to tackle several challenges simultaneously. Moreover, BG characteristics can be refined and tailored by engineering the process of fabrication, to develop mesoporous materials with the ability of drug release, or macroporous scaffolds, multilayered constructs, and composite to be used in tissue engineering and implants. In sum, the broad application of BGs in medicine due to their great features is very well foreseen. This study aims to provide an overview of the general requirements, composition, production, and impact of ion replacement on bioactive glass. We have also developed applications of bioactive glass in bone grafting, bone reconstruction, drug delivery, dental implant coatings, antibacterial agents, and soft tissue engineering, as well as future challenges and prospects.

REFERENCES

[1] D.S. Brauer, Bioactive Glasses—Structure and Properties, Angewandte Chemie International Edition 54(14) (2015) 4160-4181.

[2] E. El-Meliegy, R. van Noort, Bioactive Glasses, in: E. El-Meliegy, R. van Noort (Eds.), Glasses and Glass Ceramics for Medical Applications, Springer New York, New York, NY, 2012, pp. 221-227.

[3] A. Saatchi, A.R. Arani, A. Moghanian, M. Mozafari, Synthesis and characterization of electrospun cerium-doped bioactive glass/chitosan/polyethylene oxide composite scaffolds for tissue engineering applications, Ceramics International 47(1) (2021) 260-271.

[4] F. Xu, H. Ren, M. Zheng, X. Shao, T. Dai, Y. Wu, L. Tian, Y. Liu, B. Liu, J. Gunster, Y. Liu, Y. Liu, Development of biodegradable bioactive glass ceramics by DLP printed containing EPCs/BMSCs for bone tissue engineering of rabbit mandible defects, Journal of the Mechanical Behavior of Biomedical Materials 103 (2020) 103532.

[5] D. Zamani, F. Moztarzadeh, D. Bizari, Alginate-bioactive glass containing Zn and Mg composite scaffolds for bone tissue engineering, International Journal of Biological Macromolecules 137 (2019) 1256-1267.

[6] H. Granel, C. Bossard, L. Nucke, F. Wauquier, G.Y. Rochefort, J. Guicheux, E. Jallot, J. Lao, Y. Wittrant, Optimized bioactive glass: the quest for the bony graft, Advanced healthcare materials 8(11) (2019) 1801542.

[7] E. Steinhausen, R. Lefering, M. Glombitza, N. Brinkmann, C. Vogel, B. Mester, M. Dudda, Bioactive glass S53P4 vs. autologous bone graft for filling defects in patients with chronic osteomyelitis and infected non-unions–a single center experience, Journal of Bone and Joint Infection 6(4) (2021) 73-83.

[8] H. Zhao, G. Liang, W. Liang, Q. Li, B. Huang, A. Li, D. Qiu, D. Jin, In vitro and in vivo evaluation of the pH-neutral bioactive glass as high performance bone grafts, Materials Science and Engineering: C 116 (2020) 111249.

[9] L.L. Dai, M.L. Mei, C.H. Chu, E.C.M. Lo, Antibacterial effect of a new bioactive glass on cariogenic bacteria, Archives of Oral Biology 117 (2020) 104833.

[10] R. Sergi, D. Bellucci, R. Salvatori, G. Maisetta, G. Batoni, V. Cannillo, Zinc containing bioactive glasses with ultra-high crystallization temperature, good biological performance and antibacterial effects, Materials Science and Engineering: C 104 (2019) 109910.

[11] L.R. Rivera, A. Cochis, S. Biser, E. Canciani, S. Ferraris, L. Rimondini, A.R. Boccaccini, Antibacterial, pro-angiogenic and pro-osteointegrative zein-bioactive glass/copper based coatings for implantable stainless steel aimed at bone healing, Bioactive Materials 6(5) (2021) 1479-1490.

[12] N. Gómez-Cerezo, L. Casarrubios, M. Saiz-Pardo, L. Ortega, D. De Pablo, I. Díaz-Güemes, B. Fernández-Tomé, S. Enciso, F. Sánchez-Margallo, M. Portolés, Mesoporous bioactive glass/ε-polycaprolactone scaffolds promote bone regeneration in osteoporotic sheep, Acta biomaterialia 90 (2019) 393-402.

[13] A. Oryan, M. Baghaban Eslaminejad, A. Kamali, S. Hosseini, F.A. Sayahpour, H. Baharvand, Synergistic effect of strontium, bioactive glass and nano-hydroxyapatite promotes bone regeneration of critical-sized radial bone defects, Journal of Biomedical Materials Research Part B: Applied Biomaterials 107(1) (2019) 50-64.

[14] J. Zheng, F. Zhao, W. Zhang, Y. Mo, L. Zeng, X. Li, X. Chen, Sequentially-crosslinked biomimetic bioactive glass/gelatin methacryloyl composites hydrogels for bone regeneration, Materials Science and Engineering: C 89 (2018) 119-127.

[15] M.A. Balestriere, K. Schuhladen, K. Herrera Seitz, A.R. Boccaccini, S.M. Cere, J. Ballarre, Sol-gel coatings incorporating borosilicate bioactive glass enhance anti corrosive and surface performance of stainless steel implants, Journal of Electroanalytical Chemistry 876 (2020) 114735.

[16] R.C. Costa, J.G.S. Souza, J.M. Cordeiro, M. Bertolini, E.D. de Avila, R. Landers, E.C. Rangel, C.A. Fortulan, B. Retamal-Valdes, N.C. da Cruz, M. Feres, V.A.R. Barão, Synthesis of bioactive glass-based coating by plasma electrolytic oxidation: Untangling a new deposition pathway toward titanium implant surfaces, Journal of Colloid and Interface Science 579 (2020) 680-698.

[17] N. Rohr, J.B. Nebe, F. Schmidli, P. Müller, M. Weber, H. Fischer, J. Fischer, Influence of bioactive glass-coating of zirconia implant surfaces on human osteoblast behavior in vitro, Dental Materials 35(6) (2019) 862-870.

[18] R. Borges, K.C. Kai, C.A. Lima, D.M. Zezell, D.R. de Araujo, J. Marchi, Bioactive glass/poloxamer 407 hydrogel composite as a drug delivery system: The interplay between glass dissolution and drug release kinetics, Colloids and Surfaces B: Biointerfaces 206 (2021) 111934.

[19] Z. Tabia, K. El Mabrouk, M. Bricha, K. Nouneh, Mesoporous bioactive glass nanoparticles doped with magnesium: drug delivery and acellular in vitro bioactivity, RSC advances 9(22) (2019) 12232-12246.

[20] J. Xiao, Y. Wan, Z. Yang, Y. Huang, F. Yao, H. Luo, Bioactive glass nanotube scaffold with well-ordered mesoporous structure for improved bioactivity and controlled drug delivery, Journal of Materials Science & Technology 35(9) (2019) 1959-1965.

[21] M. Vajdi, F.S. Moghanlou, F. Sharifianjazi, M.S. Asl, M. Shokouhimehr, A review on the Comsol Multiphysics studies of heat transfer in advanced ceramics, Journal of Composites and Compounds 2(2) (2020) 35-43.

[22] F. Sharifianjazi, A.H. Pakseresht, M.S. Asl, A. Esmaeilkhanian, H.W. Jang, M. Shokouhimehr, Hydroxyapatite consolidated by zirconia: applications for dental implant, Journal of Composites and Compounds 2(2) (2020) 26-34.

[23] M.E. Astaneh, A. Goodarzi, M. Khanmohammadi, A. Shokati, S. Mohandesnezhad, M.R. Ataollahi, S. Najafipour, M.S. Farahani, J. Ai, Chitosan/gelatin hydrogel and endometrial stem cells with subsequent atorvastatin injection impact in regenerating spinal cord tissue, Journal of Drug Delivery Science and Technology 58 (2020) 101831.

[24] M. Borj, S. Taghizadehborojeni, A. Shokati, N. Sanikhani, H. Pourghadamyari, A. Mohammadi, E. Abbariki, T. Golmohammadi, S.M. Hoseiniharouni, Urinary tract infection among diabetic patients with regard to the risk factors, causative organisms and their antimicrobial susceptibility profiles at Firoozgar Hospital, Tehran, Iran, International Journal of Life Science and Pharma Research 7(3) (2017) L38-L47.

[25] A. Oryan, M. Baghaban Eslaminejad, A. Kamali, S. Hosseini, F.A. Sayahpour, H. Baharvand, Synergistic effect of strontium, bioactive glass and nano-hydroxyapatite promotes bone regeneration of critical-sized radial bone defects, Journal of Biomedical Materials Research Part B: Applied Biomaterials 107(1) (2019) 50-64.

[26] E. Steinhausen, R. Lefering, M. Glombitza, N. Brinkmann, C. Vogel, B. Mester, M. Dudda, Bioactive glass S53P4 vs. autologous bone graft for filling defects in patients with chronic osteomyelitis and infected non-unions – a single center experience, J. Bone Joint Infect. 6(4) (2021) 73-83.

[27] H. Khalilpour, P. Shafiee, A. Darbandi, M. Yusuf, S. Mahmoudi, Z.M. Goudarzi, S. Mirzamohammadi, Application of Polyoxometalate-based composites for sensor systems: A review, Journal of Composites and Compounds 3(7) (2021) 129-139.

[28] Y. Zhou, M. Shi, J.R. Jones, Z. Chen, J. Chang, C. Wu, Y. Xiao, Strategies to direct vascularisation using mesoporous bioactive glass-based biomaterials for bone regeneration, International Materials Reviews 62(7) (2017) 392-414.
[29] F. Sharifianjazi, M. Irani, A. Esmaeilkhanian, L. Bazli, M.S. Asl, H.W. Jang, S.Y. Kim, S. Ramakrishna, M. Shokouhimehr, R.S. Varma, Polymer incorporated magnetic nanoparticles: Applications for magnetoresponsive targeted drug delivery, Materials Science and Engineering: B 272 (2021) 115358.
[30] A. Moghanian, A. Ghorbanoghli, M. Kazem-Rostami, A. Pazhouheshgar, E. Salari, M. Saghafi Yazdi, T. Alimardani, H. Jahani, F. Sharifian Jazi, M. Tahriri, Novel antibacterial Cu/Mg-substituted 58S-bioglass: Synthesis, characterization and investigation of in vitro bioactivity, International Journal of Applied Glass Science 11(4) (2020) 685-698.
[31] A. Moghanian, A. Koohfar, S. Hosseini, S.H. Hosseini, A. Ghorbanoghli, M. Sajjadnejad, M. Raz, M. Elsa, F. Sharifianjazi, Synthesis, characterization and in vitro biological properties of simultaneous co-substituted Ti+4/Li+1 58s bioactive glass, Journal of Non-Crystalline Solids 561 (2021) 120740.
[32] A. Moghanian, S. Nasiripour, S.M. Hosseini, S.H. Hosseini, A. Rashvand, A. Ghorbanoghli, A. Pazhouheshgar, F. Sharifian Jazi, The effect of Ag substitution on physico-chemical and biological properties of sol-gel derived 60%SiO2-31%CaO-4%P2O5-5%TiO2 (mol%) quaternary bioactive glass, Journal of Non-Crystalline Solids 560 (2021) 120732.
[33] M.S.N. Shahrbabak, F. Sharifianjazi, D. Rahban, A. Salimi, A comparative investigation on bioactivity and antibacterial properties of sol-gel derived 58S bioactive glass substituted by Ag and Zn, Silicon 11(6) (2019) 2741-2751.
[34] F. Sharifianjazi, N. Parvin, M. Tahriri, Synthesis and characteristics of sol-gel bioactive SiO2-P2O5-CaO-Ag_2O glasses, Journal of Non-Crystalline Solids 476 (2017) 108-113.
[35] J.-a.N. Oliver, Y. Su, X. Lu, P.-H. Kuo, J. Du, D. Zhu, Bioactive glass coatings on metallic implants for biomedical applications, Bioactive Materials 4 (2019) 261-270.
[36] V.K.H. Bui, M.K. Kumar, M. Alinaghibeigi, S. Moolayadukkam, S. Eskandarinejad, S. Mahmoudi, S. Mirzamohammadi, M. Rezaei-khamseh, A review on zinc oxide composites for energy storage applications: solar cells, batteries, and supercapacitors, Journal of Composites and Compounds 3(8) (2021) 182-193.
[37] S. Ghosh, S. Nandi Majumdar, M. Shukla, Enhanced bioactive glass-ceramic coating on Ti6Al4V substrate by microwave processing technique for biomedical applications, Materials Letters 218 (2018) 60-66.
[38] S.K. Sarkar, B.T. Lee, Synthesis of bioactive glass by microwave energy irradiation and its in-vitro biocompatibility, Bioceramics Development Applications 1 (2011).
[39] M.R. Syed, N.Z. Bano, S. Ghafoor, H. Khalid, S. Zahid, U. Siddiqui, A.S. Hakeem, A. Asif, M. Kaleem, A.S. Khan, Synthesis and characterization of bioactive glass fiber-based dental restorative composite, Ceramics International 46(13) (2020) 21623-21631.
[40] N. Hild, P.N. Tawakoli, J.G. Halter, B. Sauer, W. Buchalla, W.J. Stark, D. Mohn, pH-dependent antibacterial effects on oral microorganisms through pure PLGA implants and composites with nanosized bioactive glass, Acta Biomaterialia 9(11) (2013) 9118-9125.
[41] D. Mohn, M. Zehnder, T. Imfeld, W.J. Stark, Radio-opaque nanosized bioactive glass for potential root canal application: evaluation of radiopacity, bioactivity and alkaline capacity, International Endodontic Journal 43(3) (2010) 210-217.
[42] R. Odermatt, M. Par, D. Mohn, D.B. Wiedemeier, T. Attin, T.T. Tauböck, Bioactivity and Physico-Chemical Properties of Dental Composites Functionalized with Nano- vs. Micro-Sized Bioactive Glass, Journal of Clinical Medicine 9(3) (2020).
[43] A. Esmaeilkhanian, F. Sharifianjazi, N. Parvin, M.A. Kooti, Cytotoxicity of thermoresponsive core/shell Ni x Co1− x Fe2O4/PEG nanoparticles synthesized by the sol–gel method, Journal of Physics D: Applied Physics 54(29) (2021) 295002.
[44] Z. Goudarzi, N. Parvin, F. Sharifianjazi, Formation of hydroxyapatite on surface of SiO2– P2O5–CaO–SrO–ZnO bioactive glass synthesized through sol-gel route, Ceramics International 45(15) (2019) 19323-19330.
[45] F. Sharifianjazi, N. Parvin, M. Tahriri, Formation of apatite nano-needles on novel gel derived SiO2-P2O5-CaO-SrO-Ag2O bioactive glasses, Ceramics International 43(17) (2017) 15214-15220.
[46] Z. Khurshid, S. Husain, H. Alotaibi, R. Rehman, M.S. Zafar, I. Farooq, A.S. Khan, Chapter 18 - Novel Techniques of Scaffold Fabrication for Bioactive Glasses, in: G. Kaur (Ed.), Biomedical, Therapeutic and Clinical Applications of Bioactive Glasses, Woodhead Publishing2019, pp. 497-519.
[47] P. Naresh, N. Narsimlu, C. Srinivas, M. Shareefuddin, K. Siva Kumar, Ag2O doped bioactive glasses: An investigation on the antibacterial, optical, structural and impedance studies, Journal of Non-Crystalline Solids 549 (2020) 120361.
[48] J. Singh, V. Kumar, T. Singh, Synthesis and photon interaction characterizations of some bioactive glasses, Journal of Non-Crystalline Solids 548 (2020) 120328.
[49] G. Kaur, O.P. Pandey, K. Singh, D. Homa, B. Scott, G. Pickrell, A review of bioactive glasses: their structure, properties, fabrication and apatite formation, Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 102(1) (2014) 254-274.
[50] K. Zheng, A.R. Boccaccini, Sol-gel processing of bioactive glass nanoparticles: A review, Advances in Colloid and Interface Science 249 (2017) 363-373.
[51] Z. Goudarzi, N. Parvin, F. Sharifianjazi, Formation of hydroxyapatite on surface of SiO2–P2O5–CaO–SrO–ZnO bioactive glass synthesized through sol-gel route, Ceramics International 45(15) (2019) 19323-19330.
[52] M. Montazerian, E.D. Zanotto, Bioactive and inert dental glass-ceramics, Journal of Biomedical Materials Research Part A 105(2) (2017) 619-639.
[53] F. Sharifianjazi, M. Moradi, A. Abouchenari, A.H. Pakseresht, A. Esmaeilkhanian, M. Shokouhimehr, M.S. Asl, Effects of Sr and Mg dopants on biological and mechanical properties of SiO2–CaO–P2O5 bioactive glass, Ceramics International 46(14) (2020) 22674-22682.
[54] V.S. Rizi, F. Sharifianjazi, H. Jafarikhorami, N. Parvin, L.S. Fard, M. Irani, A. Esmaeilkhanian, Sol–gel derived SnO2/Ag2O ceramic nanocomposite for H2 gas sensing applications, Materials Research Express 6(11) (2019) 1150g2.
[55] M.S. Dahiya, V.K. Tomer, S. Duhan, 1 - Bioactive glass/glass ceramics for dental applications, in: A.M. Asiri, Inamuddin, A. Mohammad (Eds.), Applications of Nanocomposite Materials in Dentistry, Woodhead Publishing2019, pp. 1-25.
[56] S. Chitra, P. Bargavi, S. Balakumar, Effect of microwave and probe sonication processes on sol–gel-derived bioactive glass and its structural and biocompatible investigations, Journal of Biomedical Materials Research Part B: Applied Biomaterials 108(1) (2020) 143-155.
[57] G. Kaur, G. Pickrell, N. Sriranganathan, V. Kumar, D. Homa, Review and the state of the art: Sol–gel and melt quenched bioactive glasses for tissue engineering, Journal of Biomedical Materials Research Part B: Applied Biomaterials 104(6) (2016) 1248-1275.
[58] E.R. Essien, V.N. Atasie, E.U. Udobang, Microwave energy-assisted formation of bioactive CaO–MgO–SiO2 ternary glass from bio-wastes, Bulletin of Materials Science 39(4) (2016) 989-995.
[59] M.A. Alam, M.H. Asoushe, P. Pourhakkak, L. Gritsch, A. Alipour, S. Mohammadi, Preparation of bioactive polymer-based composite by different techniques and application in tissue engineering: A review, Journal of Composites and Compounds 3(8) (2021) 194-205.
[60] S.K. Sarkar, A. Sadiasa, B.T. Lee, Synthesis of a novel bioactive glass using the ultrasonic energy assisted hydrothermal method and their biocompatibility evaluation, Journal of Materials Research 29(16) (2014) 1781-1789.
[61] Z. Amini, S.S. Rudsary, S.S. Shahraeini, B.F. Dizaji, P. Goleij, A. Bakhtiari, M. Irani, F. Sharifianjazi, Magnetic bioactive glasses/Cisplatin loaded-chitosan (CS)-grafted-poly (ε-caprolactone) nanofibers against bone cancer treatment, Carbohydrate Polymers 258 (2021) 117680.
[62] K. Dimitriadis, D.U. Tulyaganov, S. Agathopoulos, Development of novel alumina-containing bioactive glass-ceramics in the CaO-MgO-SiO2 system as candidates for dental implant applications, Journal of the European Ceramic Society 41(1) (2021) 929-940.
[63] F. Hmood, F. Schmidt, O. Goerke, J. Günster, Investigation of chemically modified ICIE16 bioactive glass, part II, Journal of Ceramic Science and Technology 11(1) (2019) 1-10.
[64] N.A. Al-eesa, S.D. Fernandes, R.G. Hill, F.S.L. Wong, U. Jargalsaikhan, S. Shahid, Remineralising fluorine containing bioactive glass composites, Dental Materials 37(4) (2021) 672-681.
[65] A.C. Özarslan, Y.B. Elalmis, S. Yücel, Production of biosilica based bioactive glass-alginate composite putty as bone support material, and evaluation of in vitro properties; bioactivity and cytotoxicity behavior, Journal of Non-Crystalline Solids 561 (2021) 120755.
[66] A. Moghanian, M. Zohourfazeli, M.H.M. Tajer, The effect of zirconium content on in vitro bioactivity, biological behavior and antibacterial activity of sol-gel derived 58S bioactive glass, Journal of Non-Crystalline Solids 546 (2020) 120262.
[67] M. Barczak, Functionalization of mesoporous silica surface with carboxylic groups by Meldrum's acid and its application for sorption of proteins, Journal of Porous Materials 26(1) (2019) 291-300.
[68] A. Moghanian, S. Firoozi, M. Tahriri, Synthesis and in vitro studies of sol-gel derived lithium substituted 58S bioactive glass, Ceramics International 43(15) (2017) 12835-12843.
[69] Z. Neščáková, K. Zheng, L. Liverani, Q. Nawaz, D. Galusková, H. Kaňková,

M. Michálek, D. Galusek, A.R. Boccaccini, Multifunctional zinc ion doped sol – gel derived mesoporous bioactive glass nanoparticles for biomedical applications, Bioactive Materials 4 (2019) 312-321.

[70] F. Baino, E. Fiume, M. Miola, E. Verné, Bioactive sol-gel glasses: Processing, properties, and applications, International Journal of Applied Ceramic Technology 15(4) (2018) 841-860.

[71] C.-L. Huang, W. Fang, I.H. Chen, T.-Y. Hung, Manufacture and biomimetic mineral deposition of nanoscale bioactive glasses with mesoporous structures using sol-gel methods, Ceramics International 44(14) (2018) 17224-17229.

[72] G.d.S. Balbinot, F.M. Collares, T.L. Herpich, F. Visioli, S.M.W. Samuel, V.C.B. Leitune, Niobium containing bioactive glasses as remineralizing filler for adhesive resins, Dental Materials 36(2) (2020) 221-228.

[73] G.P. Delpino, R. Borges, T. Zambanini, J.F.S. Joca, I. Gaubeur, A.C.S. de Souza, J. Marchi, Sol-gel-derived 58S bioactive glass containing holmium aiming brachytherapy applications: A dissolution, bioactivity, and cytotoxicity study, Materials Science and Engineering: C 119 (2021) 111595.

[74] A.M. Deliormanlı, B. Rahman, S. Oguzlar, K. Ertekin, Structural and luminescent properties of Er^{3+} and Tb^{3+}-doped sol–gel-based bioactive glass powders and electrospun nanofibers, Journal of Materials Science 56(26) (2021) 14487-14504.

[75] S. Heid, P.R. Stoessel, T.T. Tauböck, W.J. Stark, M. Zehnder, D. Mohn, Incorporation of particulate bioactive glasses into a dental root canal sealer, Biomedical glasses 2(1) (2016).

[76] L.A. Strobel, N. Hild, D. Mohn, W.J. Stark, A. Hoppe, U. Gbureck, R.E. Horch, U. Kneser, A.R. Boccaccini, Novel strontium-doped bioactive glass nanoparticles enhance proliferation and osteogenic differentiation of human bone marrow stromal cells, Journal of Nanoparticle Research 15(7) (2013) 1780.

[77] M. Erol Taygun, A.R. Boccaccini, 10 - Nanoscaled bioactive glass particles and nanofibers, in: H. Ylänen (Ed.), Bioactive Glasses (Second Edition), Woodhead Publishing2018, pp. 235-283.

[78] C.S. Kumar, Nanostructured oxides, John Wiley and Sons2009.

[79] A. Farzadi, M. Solati-Hashjin, F. Bakhshi, A. Aminian, Synthesis and characterization of hydroxyapatite/β-tricalcium phosphate nanocomposites using microwave irradiation, Ceramics International 37(1) (2011) 65-71.

[80] K.P. O'Flynn, B. Twomey, A. Breen, D.P. Dowling, K.T. Stanton, Microwave-assisted rapid discharge sintering of a bioactive glass–ceramic, Journal of Materials Science: Materials in Medicine 22(7) (2011) 1625-1631.

[81] V. Purcar, V. Rădiţoiu, C. Nichita, A. Bălan, A. Rădiţoiu, S. Căprărescu, F.M. Raduly, R. Manea, R. Şomoghi, C.-A. Nicolae, Preparation and Characterization of Silica Nanoparticles and of Silica-Gentamicin Nanostructured Solution Obtained by Microwave-Assisted Synthesis, Materials 14(8) (2021) 2086.

[82] H. Khalid, F. Suhaib, S. Zahid, S. Ahmed, A. Jamal, M. Kaleem, A.S. Khan, Microwave-assisted synthesis and in vitro osteogenic analysis of novel bioactive glass fibers for biomedical and dental applications, Biomedical Materials 14(1) (2018) 015005.

[83] M. Kheradmandfard, K. Mahdavi, A.Z. Kharazi, S.F. Kashani-Bozorg, D.-E. Kim, In vitro study of a novel multi-substituted hydroxyapatite nanopowder synthesized by an ultra-fast, efficient and green microwave-assisted method, Materials Science and Engineering: C 117 (2020) 111310.

[84] S.M. Rabiee, N. Nazparvar, M. Azizian, D. Vashaee, L. Tayebi, Effect of ion substitution on properties of bioactive glasses: A review, Ceramics International 41(6) (2015) 7241-7251.

[85] S. Amudha, J.R. Ramya, K.T. Arul, A. Deepika, P. Sathiamurthi, B. Mohana, K. Asokan, C.-L. Dong, S.N. Kalkura, Enhanced mechanical and biocompatible properties of strontium ions doped mesoporous bioactive glass, Composites Part B: Engineering 196 (2020) 108099.

[86] W. Hong, Q. Zhang, H. Jin, L. Song, Y. Tan, L. Luo, F. Guo, X. Zhao, P. Xiao, Roles of strontium and hierarchy structure on the in vitro biological response and drug release mechanism of the strontium-substituted bioactive glass microspheres, Materials Science and Engineering: C 107 (2020) 110336.

[87] A. Hoppe, N.S. Güldal, A.R. Boccaccini, A review of the biological response to ionic dissolution products from bioactive glasses and glass-ceramics, Biomaterials 32(11) (2011) 2757-2774.

[88] A. Moghanian, M. Zohourfazeli, M.H. Mahdi Tajer, Z. Miri, S. Hosseini, A. Rashvand, Preparation, characterization and in vitro biological response of simultaneous co-substitution of Zr+4/Sr+2 58S bioactive glass powder, Ceramics International 47(17) (2021) 23762-23769.

[89] D. Huang, F. Zhao, W. Gao, X. Chen, Z. Guo, W. Zhang, Strontium-substituted sub-micron bioactive glasses inhibit ostoclastogenesis through suppression of RANKL-induced signaling pathway, Regenerative Biomaterials 7(3) (2020) 303-311.

[90] R. Wetzel, O. Bartzok, D.S. Brauer, Influence of low amounts of zinc or magnesium substitution on ion release and apatite formation of Bioglass 45S5, Journal of Materials Science: Materials in Medicine 31(10) (2020) 86.

[91] R. Wetzel, M. Blochberger, F. Scheffler, L. Hupa, D.S. Brauer, Mg or Zn for Ca substitution improves the sintering of bioglass 45S5, Scientific Reports 10(1) (2020) 15964.

[92] A. Moghanian, S. Nasiripour, S.M. Hosseini, S.H. Hosseini, A. Rashvand, A. Ghorbanoghli, A. Pazhouheshgar, F.S. Jazi, The effect of Ag substitution on physico-chemical and biological properties of sol-gel derived 60% SiO2-31% CaO-4% P2O5-5% TiO2 (mol%) quaternary bioactive glass, Journal of Non-Crystalline Solids 560 (2021) 120732.

[93] S. Akhtach, Z. Tabia, K. El Mabrouk, M. Bricha, R. Belkhou, A comprehensive study on copper incorporated bio-glass matrix for its potential antimicrobial applications, Ceramics International 47(1) (2021) 424-433.

[94] M. Rahmani, A. Moghanian, M.S. Yazdi, The effect of Ag substitution on physicochemical and biological properties of sol-gel derived 60%SiO2–31%CaO–4%P2O5–5%Li2O (mol%) quaternary bioactive glass, Ceramics International 47(11) (2021) 15985-15994.

[95] F. Baino, Copper-Doped Ordered Mesoporous Bioactive Glass: A Promising Multifunctional Platform for Bone Tissue Engineering, Bioengineering 7(2) (2020).

[96] M. Karadjian, C. Essers, S. Tsitlakidis, B. Reible, A. Moghaddam, A.R. Boccaccini, F. Westhauser, Biological Properties of Calcium Phosphate Bioactive Glass Composite Bone Substitutes: Current Experimental Evidence, International Journal of Molecular Sciences 20(2) (2019).

[97] F.S. Rezaei, F. Sharifianjazi, A. Esmaeilkhanian, E. Salehi, Chitosan films and scaffolds for regenerative medicine applications: A review, Carbohydrate Polymers (2021) 118631.

[98] A. Moghanian, A. Koohfar, S. Hosseini, S.H. Hosseini, A. Ghorbanoghli, M. Sajjadnejad, M. Raz, M. Elsa, F. Sharifianjazi, Synthesis, characterization and in vitro biological properties of simultaneous co-substituted Ti+ 4/Li+ 1 58s bioactive glass, Journal of Non-Crystalline Solids 561 (2021) 120740.

[99] K. Dixit, N. Sinha, Compressive Strength Enhancement of Carbon Nanotube Reinforced 13-93B1 Bioactive Glass Scaffolds, Journal of nanoscience and nanotechnology 19(5) (2019) 2738-2746.

[100] K. Dixit, A. Raichur, N. Sinha, Polymer Coated and Nanofiber Reinforced Functionally Graded Bioactive Glass Scaffolds Fabricated using Additive Manufacturing, IEEE Transactions on NanoBioscience (2021).

[101] P.P. Cortez, A.F. Brito, S. Kapoor, A.F. Correia, L.M. Atayde, P. Dias-Pereira, A.C. Maurício, A. Afonso, A. Goel, J.M.F. Ferreira, The in vivo performance of an alkali-free bioactive glass for bone grafting, FastOs®BG, assessed with an ovine model, Journal of Biomedical Materials Research Part B: Applied Biomaterials 105(1) (2017) 30-38.

[102] J.D. Menezes, R.d.S. Pereira, J.P. Bonardi, G.L. Griza, R. Okamoto, E. Hochuli-Vieira, Bioactive glass added to autogenous bone graft in maxillary sinus augmentation: a prospective histomorphometric, immunohistochemical, and bone graft resorption assessment, Journal of Applied Oral Science 26 (2018).

[103] S. Zare Jalise, N. Baheiraei, F. Bagheri, The effects of strontium incorporation on a novel gelatin/bioactive glass bone graft: In vitro and in vivo characterization, Ceramics International 44(12) (2018) 14217-14227.

[104] S. Amirthalingam, S.S. Lee, M. Pandian, J. Ramu, S. Iyer, N.S. Hwang, R. Jayakumar, Combinatorial effect of nano whitlockite/nano bioglass with FGF-18 in an injectable hydrogel for craniofacial bone regeneration, Biomaterials science 9(7) (2021) 2439-2453.

[105] M.N. Gómez-Cerezo, J. Peña, S. Ivanovski, D. Arcos, M. Vallet-Regí, C. Vaquette, Multiscale porosity in mesoporous bioglass 3D-printed scaffolds for bone regeneration, Materials Science and Engineering: C 120 (2021) 111706.

[106] K. Dixit, P. Gupta, S. Kamle, N. Sinha, Structural analysis of porous bioactive glass scaffolds using micro-computed tomographic images, Journal of Materials Science 55(27) (2020) 12705-12724.

[107] K. Dixit, N. Sinha, Additive Manufacturing of Carbon Nanotube Reinforced Bioactive Glass Scaffolds for Bone Tissue Engineering, Journal of Engineering and Science in Medical Diagnostics and Therapy 4(4) (2021).

[108] C.D.F. Moreira, S.M. Carvalho, R.M. Florentino, A. França, B.S. Okano, C.M.F. Rezende, H.S. Mansur, M.M. Pereira, Injectable chitosan/gelatin/bioactive glass nanocomposite hydrogels for potential bone regeneration: In vitro and in vivo analyses, International Journal of Biological Macromolecules 132 (2019) 811-821.

[109] X. Yan, C. Yu, X. Zhou, J. Tang, D. Zhao, Highly ordered mesoporous bioactive glasses with superior in vitro bone-forming bioactivities, Angewandte Chemie International Edition 43(44) (2004) 5980-5984.

[110] A. López-Noriega, D. Arcos, I. Izquierdo-Barba, Y. Sakamoto, O. Terasaki, M. Vallet-Regí, Ordered mesoporous bioactive glasses for bone tissue regeneration, Chemistry of materials 18(13) (2006) 3137-3144.

[111] D. Arcos, M. Vallet-Regí, Sol–gel silica-based biomaterials and bone tissue

regeneration, Acta biomaterialia 6(8) (2010) 2874-2888.
[112] S. Kargozar, F. Baino, S. Hamzehlou, R.G. Hill, M. Mozafari, Bioactive glasses entering the mainstream, Drug Discovery Today 23(10) (2018) 1700-1704.
[113] S. Kargozar, M. Mozafari, S. Hamzehlou, H.-W. Kim, F. Baino, Mesoporous bioactive glasses (MBGs) in cancer therapy: Full of hope and promise, Materials Letters 251 (2019) 241-246.
[114] S. Chitra, P. Bargavi, M. Balasubramaniam, R.R. Chandran, S. Balakumar, Impact of copper on in-vitro biomineralization, drug release efficacy and antimicrobial properties of bioactive glasses, Materials Science and Engineering: C 109 (2020) 110598.
[115] F. Kurtuldu, N. Mutlu, M. Michálek, K. Zheng, M. Masar, L. Liverani, S. Chen, D. Galusek, A.R. Boccaccini, Cerium and gallium containing mesoporous bioactive glass nanoparticles for bone regeneration: Bioactivity, biocompatibility and antibacterial activity, Materials Science and Engineering: C 124 (2021) 112050.
[116] H. Reza Rezaie, H. Beigi Rizi, M.M. Rezaei Khamseh, A. Öchsner, Dental Restorative Materials, in: H. Reza Rezaie, H. Beigi Rizi, M.M. Rezaei Khamseh, A. Öchsner (Eds.), A Review on Dental Materials, Springer International Publishing, Cham, 2020, pp. 47-171.
[117] M.A. Akhtar, K. Ilyas, I. Dlouhý, F. Siska, A.R. Boccaccini, Electrophoretic Deposition of Copper (II)–Chitosan Complexes for Antibacterial Coatings, International journal of molecular sciences 21(7) (2020) 2637.
[118] J. Ballarre, T. Aydemir, L. Liverani, J.A. Roether, W. Goldmann, A.R. Boccaccini, Versatile bioactive and antibacterial coating system based on silica, gentamicin, and chitosan: Improving early stage performance of titanium implants, Surface and Coatings Technology 381 (2020) 125138.
[119] C.-Y. Chen, Y.-C. Chung, Antibacterial effect of water-soluble chitosan on representative dental pathogens Streptococcus mutans and Lactobacilli brevis, Journal of Applied Oral Science 20 (2012) 620-627.
[120] N.A. Torghabeh, B. Raissi, R. Riahifar, M. Sahbayaghmaee, Z.M. Bidgoli, Investigation of the flocculation and sedimentation of TiO2 nanoparticles in different alcoholic environments through turbidity measurements, Journal of Composites and Compounds 3(8) (2021) 159-163.
[121] K. Zheng, P. Balasubramanian, T.E. Paterson, R. Stein, S. MacNeil, S. Fiorilli, C. Vitale-Brovarone, J. Shepherd, A.R. Boccaccini, Ag modified mesoporous bioactive glass nanoparticles for enhanced antibacterial activity in 3D infected skin model, Materials Science and Engineering: C 103 (2019) 109764.
[122] R.N. Azadani, M. Sabbagh, H. Salehi, A. Cheshmi, A. Raza, B. Kumari, G. Erabi, Sol-gel: Uncomplicated, routine and affordable synthesis procedure for utilization of composites in drug delivery, Journal of Composites and Compounds 3(6) (2021) 57-70.
[123] K. Zhang, Q. Van Le, Bioactive glass coated zirconia for dental implants: a review, Journal of Composites and Compounds 2(2) (2020) 10-17.
[124] A.J. Rad, Synthesis of copper oxide nanoparticles on activated carbon for pollutant removal in Tartrazine structure, Journal of Composites and Compounds 2(3) (2020) 99-104.
[125] A. Balamurugan, G. Balossier, D. Laurent-Maquin, S. Pina, A. Rebelo, J. Faure, J. Ferreira, An in vitro biological and anti-bacterial study on a sol–gel derived silver-incorporated bioglass system, dental materials 24(10) (2008) 1343-1351.
[126] M. Bellantone, H.D. Williams, L.L. Hench, Broad-spectrum bactericidal activity of Ag2O-doped bioactive glass, Antimicrobial agents and chemotherapy 46(6) (2002) 1940-1945.
[127] A.M. El-Kady, A.F. Ali, R.A. Rizk, M.M. Ahmed, Synthesis, characterization and microbiological response of silver doped bioactive glass nanoparticles, Ceramics International 38(1) (2012) 177-188.
[128] A. Ahmed, A. Ali, D.A. Mahmoud, A. El-Fiqi, Preparation and characterization of antibacterial P2O5–CaO–Na2O–Ag2O glasses, Journal of Biomedical Materials Research Part A 98(1) (2011) 132-142.
[129] N. Baheiraei, F. Moztarzadeh, M. Hedayati, Preparation and antibacterial activity of Ag/SiO2 thin film on glazed ceramic tiles by sol–gel method, Ceramics international 38(4) (2012) 2921-2925.
[130] R.C. Lucacel, T. Radu, A. Tătar, I. Lupan, O. Ponta, V. Simon, The influence of local structure and surface morphology on the antibacterial activity of silver-containing calcium borosilicate glasses, Journal of non-crystalline solids 404 (2014) 98-103.
[131] S. Ni, X. Li, P. Yang, S. Ni, F. Hong, T.J. Webster, Enhanced apatite-forming ability and antibacterial activity of porous anodic alumina embedded with CaO–SiO2–Ag2O bioactive materials, Materials Science and Engineering: C 58 (2016) 700-708.
[132] X. Chatzistavrou, J.C. Fenno, D. Faulk, S. Badylak, T. Kasuga, A.R. Boccaccini, P. Papagerakis, Fabrication and characterization of bioactive and antibacterial composites for dental applications, Acta biomaterialia 10(8) (2014) 3723-3732.
[133] T. Waltimo, T. Brunner, M. Vollenweider, W.J. Stark, M. Zehnder, Antimicrobial effect of nanometric bioactive glass 45S5, Journal of dental research 86(8) (2007) 754-757.
[134] S. Hu, J. Chang, M. Liu, C. Ning, Study on antibacterial effect of 45S5 Bioglass®, Journal of Materials Science: Materials in Medicine 20(1) (2009) 281-286.
[135] V. Mortazavi, M.M. Nahrkhalaji, M. Fathi, S. Mousavi, B.N. Esfahani, Antibacterial effects of sol-gel-derived bioactive glass nanoparticle on aerobic bacteria, Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 94(1) (2010) 160-168.
[136] D. Zhang, O. Leppäranta, E. Munukka, H. Ylänen, M.K. Viljanen, E. Eerola, M. Hupa, L. Hupa, Antibacterial effects and dissolution behavior of six bioactive glasses, Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 93(2) (2010) 475-483.
[137] M. Vaahtio, E. Munukka, O. Leppäranta, D. Zhang, E. Eerola, H.O. Ylänen, T. Peltola, Effect of ion release on antibacterial activity of melt-derived and sol-gel-derived reactive ceramics, Key Engineering Materials, Trans Tech Publ, 2006, pp. 349-354.
[138] P. Stoor, E. Söderling, R. Grenman, Interactions between the bioactive glass S53P4 and the atrophic rhinitis-associated microorganism Klebsiella ozaenae, Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 48(6) (1999) 869-874.
[139] M. Echezarreta-López, T. De Miguel, F. Quintero, J. Pou, M. Landin, Antibacterial properties of laser spinning glass nanofibers, International journal of pharmaceutics 477(1-2) (2014) 113-121.
[140] D.S. Brauer, N. Karpukhina, G. Kedia, A. Bhat, R.V. Law, I. Radecka, R.G. Hill, Bactericidal strontium-releasing injectable bone cements based on bioactive glasses, Journal of the Royal Society Interface 10(78) (2013) 20120647.
[141] M. Zehnder, T. Waltimo, B. Sener, E. Söderling, Dentin enhances the effectiveness of bioactive glass S53P4 against a strain of Enterococcus faecalis, Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 101(4) (2006) 530-535.
[142] R. Chen, Q. Li, S. Xu, J. Han, P. Huang, Z. Yu, D. Jia, J. Liu, H. Jia, M. Shen, Nanosized HCA-coated borate bioactive glass with improved wound healing effects on rodent model, Chemical Engineering Journal (2021) 130299.
[143] K. Schuhladen, J.A. Roether, A.R. Boccaccini, Bioactive glasses meet phytotherapeutics: the potential of natural herbal medicines to extend the functionality of bioactive glasses, Biomaterials 217 (2019) 119288.
[144] F. Westhauser, B. Widholz, Q. Nawaz, S. Tsitlakidis, S. Hagmann, A. Moghaddam, A. Boccaccini, Favorable angiogenic properties of the borosilicate bioactive glass 0106-B1 result in enhanced in vivo osteoid formation compared to 45S5 Bioglass, Biomaterials science 7(12) (2019) 5161-5176.
[145] J. Zhou, H. Wang, S. Zhao, N. Zhou, L. Li, W. Huang, D. Wang, C. Zhang, In vivo and in vitro studies of borate based glass micro-fibers for dermal repairing, Materials Science and Engineering: C 60 (2016) 437-445.
[146] S. Zhao, L. Li, H. Wang, Y. Zhang, X. Cheng, N. Zhou, M.N. Rahaman, Z. Liu, W. Huang, C. Zhang, Wound dressings composed of copper-doped borate bioactive glass microfibers stimulate angiogenesis and heal full-thickness skin defects in a rodent model, Biomaterials 53 (2015) 379-391.
[147] J. Fourie, F. Taute, L. du Preez, D. De Beer, Chitosan Composite Biomaterials for Bone Tissue Engineering—a Review, Regenerative Engineering and Translational Medicine (2020) 1-21.
[148] K. Schuhladen, A.R. Boccaccini, 15 - Bioactive glass variants for tissue engineering: From the macro- to the nanoscale, in: A. Osaka, R. Narayan (Eds.), Bioceramics, Elsevier2021, pp. 353-373.
[149] M. Luginina, K. Schuhladen, R. Orrú, G. Cao, A.R. Boccaccini, L. Liverani, Electrospun PCL/PGS Composite Fibers Incorporating Bioactive Glass Particles for Soft Tissue Engineering Applications, Nanomaterials 10(5) (2020).
[150] I. Holland, J. Logan, J. Shi, C. McCormick, D. Liu, W. Shu, 3D biofabrication for tubular tissue engineering, Bio-design and Manufacturing 1(2) (2018) 89-100.
[151] S. Naseri, W.C. Lepry, S.N. Nazhat, Bioactive glasses in wound healing: hope or hype?, Journal of Materials Chemistry B 5(31) (2017) 6167-6174.
[152] D.C. Lobb, B.R. DeGeorge, Jr., A.B. Chhabra, Bone Graft Substitutes: Current Concepts and Future Expectations, The Journal of hand surgery 44(6) (2019) 497-505.e2.
[153] D. Fernando, N. Attik, N. Pradelle-Plasse, P. Jackson, B. Grosgogeat, P. Co-

lon, Bioactive glass for dentin remineralization: A systematic review, Materials Science and Engineering: C 76 (2017) 1369-1377.